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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,501	WOLFFE ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *123-152* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *123-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement filed newly filed now contains the cited references and is attached, initialed.

Claim interpretation

2. In claim 122, the term "library" is broadly interpreted as including any collection of nucleic acids, since any collection of nucleic acids can comprise a nucleic acid library. Further, the term "probe" in claim 143 is broadly interpreted to include any molecule, including a nuclease such as "DNAseI".

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 123-128, 130, 135, 143-145 and 147-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grosveld et al (U.S. Patent 5,635,355).

Grosveld teaches a method of preparing nucleic acids which comprise regulatory sequences from a cell (see column 21, claim 1, line 1, for example), comprising the steps:

a) providing a cell nucleus, wherein the nucleus comprises cellular chromatin (see column 8, lines 1-17, where nucleic of HEL and PUTKO cells are used),

b) contacting the nucleus with DNAse I, wherein the DNAseI reacts with accessible regions of cellular chromatin (see column 8, lines 17-21),

c) deproteinizing the cellular chromatin to generate deproteinized DNA (see column 8, lines 22-23, treatment with proteinase K),

d) contacting the deproteinized DNA with a second enzyme to generate DNA fragments (see column 8, lines 23-25, where the DNA was recut with Asp718).

e) contacting DNA fragments of interest that contain DNAse I hypersensitive sites with a population of vectors, to permit ligation of the DNA fragments to the vectors (see column 15, lines 43-47 and column 21, lines 18-20, claim 1),

f) selecting polynucleotides comprising a DNA fragment ligated to a vector molecule (see column 15, lines 43-47 and column 21, lines 18-20, claim 1).

With regard to claim 124, Grosveld teaches the use of animal cells (see column 8, lines 1-17).

With regard to claims 125-126, Grosveld teaches the use of DNAse I (see column 8, lines 17-21).

With regard to claims 127-128, Grosveld teaches the use of a restriction enzyme (see column 8, lines 23-25).

With regard to claim 130, Grosveld teaches BamHI (see column 13, line 57).

With regard to claim 135, Grosveld teaches preparation from different cell types (see column 8, lines 1-17).

With regard to claims 143-144, Grosveld teaches detection of the hypersensitive site with a nuclei acid probe (see column 8, lines 43-47) prior to cleavage as well as with a DNAseI probe which necessarily interacts prior to cleavage (see column 8, lines 17-21).

With regard to claim 145, Grosveld teaches the use of an isolated nucleus (see column 8, lines 1-17).

With regard to claims 147-148, 150, Grosveld teaches the use of DNAseI, (see column 8, lines 17-21).

With regard to claim 149, 151, Grosveld teaches the use of restriction enzymes (see column 8, lines 23-25).

Grosveld does not exemplify the cloning of the DNAseI hypersensitive fragment formed in column 8 into a vector as taught by claim 1. However, Grosveld expressly teaches and suggests cloning of DNAseI hypersensitive site DNA fragments (see claim 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Grosveld to clone the DNAseI hypersensitive fragments identified in column 8 of Grosveld since Grosveld expressly claims "A method of obtaining a DNA fragment comprising a dominant activator sequence, comprising 1) providing a candidate DNA fragment comprising a DNase I hypersensitive site from a genetic locus containing a structural gene that is expressed in a manner that is specific for a particular mammalian cell type; 2) ligating the fragment to an expressible gene to form a construct. (see claim 1)." So Grosveld expressly states that DNAseI hypersensitive sites, such as those identified by the method taught by Grosveld, should be ligated into a vector in claim 1. Grosveld provides the motivation in claim 1 as well, indicated that the resultant vector can be used to provide expression of a transgene that is independent of the integration site of the vector into the host cell genome. Thus, Grosveld in column 1 identifies a problem in gene therapy, which is that integration of vectors into some sites will prevent gene expression. Grosveld teaches that this problem can be solved by cloning DNAseI hypersensitive sites into cloning vectors, which sites are associated with expression independent of the integration site. Therefore, an ordinary practitioner would have been motivated to clone the DNA fragments obtained by Grosveld as DNAseI hypersensitive sites into cloning vectors since Grosveld expressly claims such cloning and since Grosveld expressly teaches that such cloning can result in integration site independent expression.

6. Claims 129, 131-133 and 152 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grosveld in view of NEB catalog (1995), pages 32, 46, 48 and 83.

Grosveld teaches the limitations of claims 123-128, 130, 135, 143-145 and 147-151 as discussed above. Grosveld does not teach all of the restriction enzymes, whether sticky or blunt ended, that can be used in the method, nor does Grosveld teaches formation of blunt ends after DNAse digestion.

NEB catalog teaches Sau3AI (see page 46), required for claims 129 and 152. NEB catalog also teaches EcoRV and SmaI (see pages 32 and 48). Finally, NEB catalog teaches the use of Mung bean nuclease to form blunt ends for ligation into vectors (see page 83).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Grosveld to use the equivalent enzymes and ligation methods taught by NEB catalog since the enzymes in the NEB catalog and the methods of ligation are all known equivalents of the enzymes and methods used by Grosveld, as evidenced by the NEB catalog. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

7. Claims 136-142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grosveld in view of Li et al (U.S. Patent 5,500,356).

Grosveld teaches the limitations of claims 123-128, 130, 135, 143-145 and 147-151 as discussed above. Grosveld does not teach comparison of cells from a variety of different sources.

Li teaches isolation of nucleic acids from "a homogeneous specimen (such as cells in tissue culture, cells of the same tissue, etc.), or a heterogeneous specimen (such as a mixture of pathogen-free and pathogen-infected cells, a mixture of cells of different tissues, species, or cells of the same or different tissue at different temporal or developmental stages, etc.). The cells, if any, of these nucleic acid sources may be either prokaryotic or eukaryotic cells (such as those of animals, humans and higher plants) (see column 5, lines 42-50)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Grosveld to use the variety of cell types taught by Li since an ordinary practitioner using the method of Grosveld would be motivated to obtain dominant activator sequences from any naturally occurring gene system (see column 4, lines 39-45) so Grosveld would be motivated to identify such dominant activator sequences in all tissues since every tissue is a target for some genetic therapy related to a disease in that tissue and Grosveld recognizes that such therapies require that a stably inserted gene therapy vector be expressed irrespective of location within the chromosome (see column 4). So an ordinary practitioner would have

been motivated to use the multiple cell types taught by Li to screen for dominant activators in order to obtain dominant activators which function in a wide variety of cell types as suggested by Grosveld (see column 4, lines 39-45).

8. Claims 134 and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grosveld in view of Chung et al (U.S. Patent 6,444,421).

Grosveld teaches the limitations of claims 123-128, 130, 135, 143-145 and 147-151 as discussed above. Grosveld does not teach embedding the cells in agarose.

Chung teaches embedding the cells in agarose prior to enzymatic cleavage (see column 33, lines 55-57).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Grosveld to embed the cells in agarose as taught by Chung since Chung expressly teaches that "In order to minimize shearing which can produce unwanted background of cleaved sites, the genomic DNA is isolated while the cells are embedded in an agarose plug. After purification, agarose-embedded genomic DNA is digested ... (see column 33, lines 54-57)." Thus, an ordinary practitioner performing the enzymatic cleavage and cloning method of Grosveld would have been motivated to embed the nucleic in agarose in order to minimize shearing that could produce unwanted background of false positive DNAseI hypersensitive sites as expressly taught by Chung.

Response to Arguments

9. Applicant's arguments filed March 1, 2004 have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant argues that there is no suggestion in Grosveld to make "libraries", placing heavy weight on the term "libraries". However, as noted in the initial action under the claim interpretation heading, the word "library" does not carry the weight meant by Applicant. A nucleic acid "library" is simply a cloned set of nucleic acids. So when Grosveld teaches cloning of the target nucleic acid into a vector, Grosveld is forming "library". This is the central point of the rejection and the central point on which all of Applicant's arguments fall. Applicant begins and concludes by placing heavy weight on the term "library". MPEP 2111 notes "During patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification." In this case, the specification, which has an extensive definition section, does not define the term "library". So the broadest reasonable interpretation of a

nucleic acid library is a cloned set of nucleic acids. Grosveld teaches and suggests cloned sets of nucleic acids, and this is what renders the claims obvious.

Applicant then argues that Grosveld is not preparing the library to obtain sets of regulatory sequences. This argument is not relevant to the claims because Grosveld teaches and suggests the same method, even if the reason to perform the method is different. As MPEP 2144 notes "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant."

Applicant then argues that the rejection constitutes a "picking and choosing" from within Grosveld. It is quite clear that Grosveld contemplates using DNAseI hypersensitive sites into vectors as shown in column 15, where Grosveld clones these elements. There is no "picking and choosing" here, but rather a simple set of instructions provided by Grosveld on how to construct vectors with DNAse I hypersensitive sites by using a method that includes all of the steps of Applicant's claimed method, but in the prior art.

Applicant does not separately argue the remaining rejections but relies upon overcoming Grosveld. Since Grosveld is maintained, so are the other rejections.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman

JEFFREY FREDMAN
PRIMARY EXAMINER